REMARKS

STATUS OF THE CLAIMS:

Claims 1 to 40, and Claims 48 and 49 are cancelled.

Claims 41, 50, 51, 52, 58, 62, 63, 64, and 66 have been amended.

Claims 41 to 47, and 50 to 66 are pending.

Claim 41(f) has been amended to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to clarify the activity originally intended by Applicants as well as to further clarify that only the complimentary sequence of the hybridized sequence would be expected to encode a pro-apoptotic polypeptide. Support for these amendments may be found in the paragraph beginning on page 156, line 25 and continuing onto page 157, Example 5, pages 61 to 63, pages 141 to 158, and throughout the specification as originally filed. These amendments were not made to overcome any issues related to the patentability of these claims. Applicants right to equivalents of Claim 41(f) is reserved. No new matter has been added.

Claim 41 has been further amended to delete clause (d). As a consequence of this amendment, Claim 41(e) and (f) were amended to place these clauses in their proper alphabetical context in consideration of the deletion of clause (d). Specifically, the name of clause "(e)" was changed to "(d)", while the name of clause "(f)" was changed to "(e)". In addition, the phrase "or (d)" was deleted from the former clause (e), and the term "or" was added in between clause (b) and (c) of this same clause. In addition, the phrase "(a)-(e)" of the former clause (f) was changed to "(a)-(c)". These amendments were not made to overcome any issues related to the patentability of these claims. Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

Claim 50 was amended to replace the phrase "(e)" to "(d)" in order to take into consideration the change in identity of this clause in the amendment of Claim 41 described *supra*. This amendment was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claim 50 is reserved. No new matter has been added.

Claim 51 was amended to replace the phrase "(f)" to "(e)" in order to take into consideration the change in identity of this clause in the amendment of Claim 41 described *supra*. This

amendment was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claim 51 is reserved. No new matter has been added.

Claim 52 was amended to delete the phrase "(d), " and to replace the phrase "(f)" with "(e)" in order to take into consideration the change in identity of this clause in the amendment of Claim 41 described *supra*. This amendment was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claim 52 is reserved. No new matter has been added.

Claims 58, 62, 63, and 66 have been amended to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Support for these amendments may be found in the paragraph beginning on page 156, line 25 and continuing onto page 157, Example 5, pages 61 to 63, pages 141 to 158, and throughout the specification as originally filed. These amendments were not made to overcome any issues related to the patentability of these claims. Applicants right to equivalents of Claims 58, 62, 63, and 66 is reserved. No new matter has been added.

Claim 62 was further amended to append the limitation "(a)" to the Claim 41 reference in proper recognition that the polynucleotide embraced by Claim 41, clause (a), comprises amino acid 1 of SEQ ID NO:6, while the polynucleotides embraced by Claim 41, clauses (b) and (c) do not. This amendment was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claim 62 is reserved. No new matter has been added.

Claim 64 has been amended to replace the phrase "(e)" with "(d)" in order to take into consideration the change in identity of this clause in the amendment of Claim 41 described *supra*. This amendment was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claim 64 is reserved. No new matter has been added.

I. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected 41 to 66 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that these claims stand rejected "for lack of utility, for reasons set forth in Paper No: 11. Applicant's arguments filed on 8/06/03 in reference to claims 41-63 have been fully considered but they are not persuasive". The Examiner states that the arguments presented by Applicants in the August 6th, 2003 communication "are not persuasive for the following reasons. (1)Amino acid sequence identity to other TNF proteins is not sufficient for establishing utility because structural analogy to a known compound with a known activity and utility is not sufficient evidence of utility for the claimed compound (see *Brennerv. Manson,* 148 U.S.P.Q. 689 (Sus. Ct, 1966)). (2) Conservation of an TNF family domain does not provide a specific, substantial and credible utility for the claimed compound because not all of the TNF proteins of the family have the same utility. In other words, conservation of structure does not result in sufficient conservation of function to support having the same utility.".

Applicants disagree and point out that the Examiners continued rejection of Claims 41 to 66 under 35 U.S.C. § 101 on the basis that the homology to proteins with known activity and conservation of critical domains is misguided and in error. As Applicants pointed out in their August 6th, 2003 communication, Applicants specification correctly identified the protein class to which the DmTNFv2 molecule belongs (i.e., a "tumor necrosis factor molecule"); and correctly described the biological role of the claimed DmTNFv2 polynucleotides in Drosophila (i.e., involved in "modulating the innate immune response in invertebrates, particularly flies, and most preferably in Drosophila"); and correctly described the pathway in which the claimed DmTNFv2 polynucleotides are involved (i.e., the Jun N-terminal protein kinases (JNK) pathway as well as the Rel pathway). The fact that the DmTNFv2 molecule was first identified as a TNF molecule on the basis of its homology to known TNF proteins, and the fact that subsequent biochemical experiments described in Applicants specification demonstrated unequivocally that DmTNFv2 is a TNF protein, provides clear evidence that the identification of proteins on the basis of their homology to known proteins is a valid and art accepted means of identifying proteins and predicting their biochemical role. Applicants request the Examiner acknowledge that exceptions clearly exist for homology

predictions, as evidenced by the instant specification relative to DmTNFv2, and provide corrective statements in his response in an effort to correct the record.

However, as Applicants noted in the August 6th, 2003 communication, the function of the DmTNFv2 molecule described in the specification was not solely based upon its homology to other known TNF molecules. Rather, the biological role of DmTNFv2 was also based upon biochemical evidence that was disclosed in the instant specification. Specifically, Applicants provided biochemical evidence supporting the role of DmTNFv2 as a Drosophila TNF molecule by disclosing data demonstrating that DmTNFv2 is negatively regulated by Rel proteins, and evidence that low levels of DmTNFv2 expression leads to lethality. Applicants also point out that the instant specification described the basis for the lethality phenotype in the paragraph beginning on line 25 of page 156 which states that "overexpression of DmTNF induces apoptosis in Drosophila".

Although Applicants believed the teachings of the instant specification, including the biochemical data disclosed therein, was sufficient to demonstrate that the DmTNFv2 polynucleotides had utility, Applicants also brought to the Examiners attention two post-filing publications, namely Igaki et al (EMBO 21 (12):3009-3018 (2002)) and Moreno et al (Curr. Biol., 12:1263-1268 (2002), that directly corroborated the teachings of Applicants specification regarding the identity of the DmTNFv2 molecule as representing a TNF molecule, its role in modulating innate immunity in Drosophila, its modulation of the Jun N-terminal protein kinases (JNK) pathway, and its ability to induce apoptosis. Yet, despite the strong teachings of Applicants specification, including the supporting biochemical data described therein, in addition to the corroborating support of the post-filing publications of Igaki et al and Moreno et al, the Examiner still maintains that the claimed DmTNFv2 molecules lack utility.

Applicants again remind the Examiner that PTO personnel must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. In this instance, the Examiner has not brought forth any countervailing evidence that would form a legitimate basis for doubting the credibility of Applicants asserted utility. Rather, the two post-filing publications of Igaki et al and Moreno et al directly support Applicants assertions. Since, the Examiner cannot simply provide his/her opinion on whether an asserted utility is credible, and the fact that the art, vis-à-vis two independent peer reviewed journals, directly supports Applicants asserted utilities, clearly evidences the fact that the Examiner is not operating in according with U.S. patent law, its judicial precedence, nor the

guidance provided by the Office's Revised Utility Examination Guidelines. In consideration of the latter, and in conjunction with the arguments presented herein as well as in Applicants August 6th, 2003 communication, Applicants believe the Examiners continued rejection of Claims 41 to 66 under 35 U.S.C. § 101 is in error and request that the Examiner withdraw the rejection.

Although Applicants believe the teachings of the instant specification, including the supporting biochemical data described therein, in addition to the corroborating support of the post-filing publications of Igaki et al and Moreno et al, is sufficient to demonstrate that the DmTNFv2 molecule has utility, Applicants submit herewith a Declaration under Rule 132 (the "Carroll Declaration"), that provides additional proof that DmTNFv2 is a TNF molecule, that overexpression of DmTNFv2 results in apoptosis, that DmTNFv2 is involved in the JNK pathway, that the function of DmTNFv2 is directly analogous to the function of mammalian TNF, and the fact that DmTNFv2 is involved in the modulation of Drosophila innate immunity through its tightly controlled negative regulation by Rel. Applicants assert that the claimed DmTNFv2 polynucleotides meet the utility requirement and have a specific, substantial, and credible utility.

As further evidence that the claimed DmTNFv2 polynucleotides meet the utility requirement, Applicants specification clearly teaches that overexpression of DmTNFv2 results in the incidence of apoptosis (see paragraph beginning on line 25, page 156) and also that "the insect DmTNF genes and proteins in an activated form have application as "cell death" genes which if delivered to or expressed in specific target tissues such as the gut, nervous system, or gonad, would have a use in controlling insect pests" (same paragraph beginning on line 25, page 156 and continuing onto page 157).

Such a utility is specific since it is specific to controlling Drosophila infestation. Such a utility is substantial since control of Drosophila infestation represents a "real-world" context of use. Such a utility is also credible in consideration of the teachings of Applicants specification in conjunction with knowledge in the art.

The Examiner has also alleged that Applicants have not "established a nexus between DmTNFv2 proteins and immune diseases". Applicants disagree and point out again that one skilled in the art of immunology and invertebrate genetics, upon reviewing the totality of the evidence taught by the specification, would credibly believe that the DmTNFv2 is a TNF family member and would have the asserted utilities. Moreover, Applicants also assert that based upon the biochemical evidence disclosed in the instant specification that DmTNFv2 is negatively modulated by Rel, one skilled in the art would associate mis-expression of DmTNFv2 with the incidence of fungal

infections in adult Drosophila based upon knowledge readily accessible to the skilled artisan prior to Applicants filing date. Specifically, Lemaitre et al (Cell, 86:973-983 (1996); submitted concurrently herewith) demonstrate that the Drosophila proteins, dorsal and toll, which are signaling molecules in the Rel pathway, are directly associated with modulation of drosomycin gene expression, an endogenous antifungal peptide in Drosophila. Lemaitre et al show that the extracellular Toll ligand, spatzle, control expression of the antifungal peptide gene drosomycin in adults, and that mutations in the Toll signaling pathway dramatically reduce survival after fungal infection of the fungus A. fumigatus. Lemaitre et al also evidences the knowledge of the skilled artisan prior to Applicants filing date regarding the strong parallels between mammalian and Drosophila immune responses. Based in part upon this knowledge in the art, the teachings of Lemaitre et al, and in conjunction with the teachings of Applicants specification, in addition to the biochemical evidence demonstrating that DmTNFv2 is negatively modulated by Rel, Applicants assert that one skilled in the art would readily appreciate that mis-espression of DmTNFv2 could credibly result in a decreased immune response in adult Drosophila, and to the subsequent incidence of A. fumigatus infections in adult Drosophila.

Moreover, the association of DmTNFv2 to toll and dorsal modulation, and indirectly to the incidence of A.fumigatus infections in Drosophila, is consistent with the biochemical evidence outlined in Applicants specification (see Figure 9) and reconfirmed in the Carroll Declaration (see Exhibit E). Specifically, Applicants specification and the Carroll Declaration demonstrate that the ventral DmTNFv2 expression in Drosophila embryos is lost in Toll mutant (TI3 mutant) embryos, and that DmTNFv2 is shown to be expressed throughout the embryo and completely loses the ventral-specific expression in dorsal null mutants. These results clearly demonstrate that DmTNFv2 is negatively modulated by the Rel pathway, and specifically, that DmTNFv2 is modulated by Toll and dorsal, either directly or indirectly. In addition, Lemaitre et al teach that loss of function in any genes extending in the dorsoventral regulatory cascade results in a markedly impaired induction of the drosomycin gene, and hence the flies ability to combat bacterial and/or fungal infections (see Discussion). Clearly, DmTNFv2 is dorsoventrally regulated, either directly or indirectly by Toll and dorsal. Based upon these teachings, and in conjunction with the teachings of Lemaitre et al., Applicants assert that one skilled in the art would credibly associate mis-expression of DmTNFv2 with a decreased immune response in adult Drosophila, and to the subsequent incidence of A. fumigatus infections in adult Drosophila.

Applicants specification clearly supports the utility of DmTNFv2 in the impairment of fungal immunity in Drosophila (see pages 171 – 172), as well as supporting the utility of using DmTNFv2 as a pesticide as a means of controlling Drosophila infestation (see *supra*).

Applicants assert that such a use of DmTNFv2 represents a specific utility, since it is specific to fungal disorders and not just any disorder. Such a utility is substantial since it would constitute a "real-world" context of use. Specifically, modulation of DmTNFv2 could lead to significant mortality of Drosophila adults, vis-à-vis the incidence of fungal infections, which would serve as an effective pesticide since "insects could not survive an infection when antimicrobial gene induction was impaired...because they were unable to control the proliferation of the microorganisms" (see Discussion in Lemaitre et al).

Applicants assert that the claimed DmTNFv2 polynucleotides have patentable utility and request that the Examiner withdraw the rejection of Claims 41 to 66 under 35 U.S.C. § 101 in consideration of Applicants arguments provided herein, the arguments originally provided in Applicants August 6th, 2003 communication, the totality of evidence provided in Applicants specification as originally filed, in conjunction with the corroborative teachings of Igaki et al and Moreno et al, in addition to the supporting evidence submitted herewith within the Carroll Declaration.

II. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41-66 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility and that one skilled in the art clearly would not know how to use the claimed invention.

Applicants disagree and believe the Examiners rejection of Claims 41 to 66 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of Applicants arguments provided herein, the arguments originally provided in Applicants August 6th, 2003 communication, the totality of evidence provided in Applicants specification as originally filed, in conjunction with the corroborative teachings of Igaki et al and Moreno et al, in addition to the supporting evidence submitted herewith within the Carroll Declaration. Applicants respectfully request that the Examiner withdraw this rejection.

III. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41, 46, 48, 50, 51, 58 to 60, and 64 to 66 under 35 U.S.C. § 112, first paragraph, alleging that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges that Applicants "contemplate isolating polynucleotides that hybridize under stringent conditions to nucleotides that encode various regions of SEQ ID NO: 6 and also polynucleotide sequences which are at least 80% identical to those isolated from claim 41 and have a TNF activity. It is unclear from the recitation what TNF activity is contemplated in the instant invention".

Applicants disagree with the Examiners allegation and assert that the instant specification provides an adequate description to demonstrate that Applicants were in possession of sequences embraced by Claims 41, 46, 48, 50, 51, 58 to 60, and 64 to 66 for the reasons specified in Applicants August 6th, 2003 communication. However, in the interest if facilitating prosecution, Applicants have amended Claims 58, and 66 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Moreover, Applicants have amended Claim 41(f) to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to clarify the activity originally intended by Applicants as well as to further clarify that only the complimentary sequence of the hybridized sequence would be expected to encode a pro-apoptotic polypeptide. Applicants believe these amendments overcome the Examiners rejection of Claims 41(f), 58, and 66 relative to "TNF activity" and request that the rejection of these claims be withdrawn accordingly.

The Examiner also alleges that "In addition, it is also unclear what regions of the polypeptide are required to confer this activity". As Applicants pointed out in the August 6th, 2003 communication, the specification as originally filed provides adequate teachings to demonstrate to the skilled artisan that Applicants knew which regions of the DmTNFv2 polypeptide are required for its "pro-apoptic" activity and were in possession of sequences comprising this activity.

Applicants again point out to the Examiner that the specification as originally filed specifically provides the location of the TNF domain for DmTNFv2 (see pages 58 to 63, Figures 3A-C, and the figure legend for Figures 3A-C on page 11), and assert that one skilled in the art would readily appreciate that the TNF domain is critical to maintaining the pro-apoptotic activity of any TNF molecule, inclusive of DmTNFv2. The Carroll Declaration submitted herewith also makes affirmative statements relative to the same on page 2, section 4, by stating the "DmTNFv2 has the structural similarities associated with TNF molecules including a distinct C-terminal TNF domain and a hydrophobic transmembrane domain, the main features of all TNF molecules".

Applicants believe the Examiners rejection of Claim 46 under this section is in error since this claim is specific to the polynucleotides encoding the mature DmTNFv2 polypeptide. In the final office action, mailed December 2, 2003, the Examiner states that Applicants arguments regarding the rejection to the recitation of "mature polypeptide" was found persuasive in overcoming the 112, first paragraph rejections to the same. Moreover, Applicants specification explicitly supports the amino acid locations of the mature DmTNFv2 polypeptide as well as the nucleotide positions of the encoding polynucleotide of the mature DmTNFv2 polypeptide (see page 51). Applicants respectfully request that the Examiner withdraw the rejection of Claim 46 under 112, first paragraph in consideration of this error and the arguments provided herein.

Applicants do not agree with the Examiners rejection of Claim 48 under this title since Applicants clearly identified the location of the TNF domain which is explicitly denoted in Figures 3A-C as well as the legend of Figures 3A-C on page 11. Nonetheless, in the sole interest of facilitating prosecution, Applicants have cancelled Claim 48, its dependent Claim 49, as well as subpart (d) of Claim 41. Applicants believe the Examiners rejection of Claim 48 and Claim 41, in part, has been rendered moot in consideration of these cancellations.

Applicants also believe that the Examiners rejection of Claim 50, and also Claim 41(e) has also been rendered moot in consideration of Applicants deletion of clause (d) of Claim 41. Applicants point out that the Examiners original rejections specific to Applicants "complimentary sequence" claims were overcome in consideration of the arguments provided by Applicants in the August 6th, 2003 reply. Since the Claim 50 is dependent upon Claim 41(e), the fact that Claim 41(e) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly or implicitly in the Examiners current and/or prior communications, Applicants believe the

Examiners rejection of Claim 50 and Claim 41(e) has been overcome in consideration of Applicants deletion of clause (d) of Claim 41.

Applicants also believe that the Examiners rejection of Claim 51, and also Claim 41(f) has also been rendered moot in consideration of Applicants deletion of clause (d) of Claim 41, as well as Applicants amendment of Claim 41(f) to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed". Nonetheless, in an effort to further facilitate prosecution, Applicants have amended the phrase "(a)-(e)" of clause (f) of Claim 41 to recite the phrase "(a)-(c)". Since Claim 51 is dependent upon Claim 41(f), the fact that Claim 41(f) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly or implicitly in the Examiners current and/or prior communications, Applicants believe the Examiners rejection of Claim 51 and Claim 41(f) has been overcome in consideration of Applicants deletion of clause (d) of Claim 41 as well as the amendments presented *supra*.

Applicants believe the Examiners rejection of Claims 58 to 60 have also been overcome in consideration of the amendment to Claim 58 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" as well as the arguments presented *supra*. Applicants believe the specification provides adequate teachings to demonstrate to a skilled artisan that Applicants were in possession of the polynucleotides embraced by this claim as outlined in the arguments presented in Applicants August 6th, 2003 Reply. Since Claims 59 and 60 dependent from Claim 58, Applicants believe the Examiners rejection of Claims 59 and 60 have also been overcome.

Applicants believe the Examiners rejection of Claims 64 to 65 have also been overcome in consideration of Applicants deletion of clause (d) of Claim 41. Applicants point out that the Examiners original rejections specific to Applicants "complimentary sequence" claims were overcome in consideration of the arguments provided by Applicants in the August 6th, 2003 reply. Since Claim 64 is dependent upon Claim 41(e), the fact that Claim 41(e) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly or implicitly in the

Examiners current and/or prior communications, Applicants believe the Examiners rejection of Claim 64 has been overcome in consideration of Applicants deletion of clause (d) of Claim 41.

IV. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41, 46, 48, 50, 51, 58 to 60, and 64 to 66 under 35 U.S.C. § 112, first paragraph, alleging as containing subject matter which was not enabled. More particularly, the Examiner alleges that Applicants "contemplate isolating polynucleotides that hybridize under stringent conditions to nucleotides that encode various regions of SEQ ID NO: 6 and also polynucleotide sequences which are at least 80% identical to those isolated from claim 41 and have a TNF activity. It is unclear from the recitation what TNF activity is contemplated in the instant invention. In addition, it is also unclear what regions of the polypeptide are required to confer this activity. The specification only describes a single polypeptide and fails to teach or describe any other molecules that meet the structural limitations of the claims. The breadth of the claims is such that the claims encompass polypeptides from other species and related polypeptides that have yet to be described. There is a lack of guidance or teaching regarding structure and function of the polypeptide because there is only a single example of a polypeptide provided in the specification and because there is no guidance found in the prior art for this specific polypeptide.
".

Applicants disagree with the Examiners allegation and assert that the instant specification provides an adequate description to enable one skilled in the art to make and use the sequences embraced by Claims 41, 46, 48, 50, 51, 58 to 60, and 64 to 66 for the reasons specified in Applicants August 6th, 2003 communication. However, in the interest of facilitating prosecution, Applicants have amended Claims 58, and 66 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Moreover, Applicants have amended Claim 41(f) to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to clarify the activity originally intended by Applicants as well as to further

clarify that only the complimentary sequence of the hybridized sequence would be expected to encode a pro-apoptotic polypeptide. Applicants believe these amendments overcome the Examiners rejection of Claims 41(f), 58, and 66 relative to "TNF activity" and request that the rejection of these claims be withdrawn accordingly.

The Examiner also alleges that "In addition, it is also unclear what regions of the polypeptide are required to confer this activity". As Applicants pointed out in the August 6th, 2003 communication, the specification as originally filed provides adequate teachings to demonstrate to the skilled artisan that Applicants knew which regions of the DmTNFv2 polypeptide are required for its "pro-apoptic" activity. Applicants again point out to the Examiner that the specification as originally filed specifically provides the location of the TNF domain for DmTNFv2 (see pages 58 to 63, Figures 3A-C, and the figure legend for Figures 3A-C on page 11), and assert that one skilled in the art would readily appreciate that the TNF domain is critical to maintaining the pro-apoptotic activity of any TNF molecule, inclusive of DmTNFv2. The Carroll Declaration submitted herewith also makes affirmative statements relative to the same on page 2, section 4, by stating the "DmTNFv2 has the structural similarities associated with TNF molecules including a distinct C-terminal TNF domain and a hydrophobic transmembrane domain, the main features of all TNF molecules".

Regarding the Examiners allegation that Applicants specification "only describes a single polypeptide and fails to teach or describe any other molecules that meet the structural limitations of the claims", Applicants disagree and point out that Applicants specification does, in fact, describe more than one molecule that meets the structural limitations of the Claims. Specifically, Applicants specification explicitly describes the sequences of all N- and C-terminal deletion mutants of the DmTNFv2 polypeptide (see pages 55 to 59). In addition, Applicants specification also explicitly describes the sequences of both conservative and non-conservative substitution mutants of the DmTNFv2 polypeptide (see pages 59 to 60). Applicants point out that many of these deletion mutants and all of the substitution mutants fall within 80% identity of the claimed DmTNFv2 polynucleotides – thus meeting the "80% identity" limitation of Claim 58. Specifically, there are approximately 80 N-terminal deletion mutants (e.g., 409 amino acids multiplied by 20%) that are within the 80% limitation of Claim 58; there are approximately 80 C-terminal deletion mutants (e.g., 409 amino acids multiplied by 20%) that are within the 80% limitation of Claim 58; and there are approximately 320 or more amino acid substitution mutants that are within the 80% limitation disclosed explicitly in Applicants specification (e.g., 16 amino acids (332 – 316) multiplied by 20

total amino acids). Clearly, Applicants specification discloses a sufficient number of species to properly describe the genus embraced by these claims. Since polynucleotides are simultaneously reduced to practice once they are conceived (see Fiers v. Revel, 984 F.2d, 1164 (Fed. Cir. 1993)), Applicants point out that the skilled artisan only requires the sequences of a molecule to actually make and use the same. Moreover, since Applicants have clearly taught and demonstrated that the DmTNFv2 molecule has "pro-apoptotic activity" (see page 157 and Example 4), and since Applicants specification clearly teaches how to assess whether a given molecule within the breadth of these claims has "pro-apoptotic activity" (see 81 to 99), Applicants assert that one skilled in the art could easily make and use the polynucleotides embraced by these claims since it would be routine to assess if a molecule has "pro-apoptotic activity".

Applicants believe the Examiners rejection of Claim 46 under this section is in error since this claim is specific to the polynucleotides encoding the mature DmTNFv2 polypeptide. In the final office action, mailed December 2, 2003, the Examiner states that Applicants arguments regarding the rejection to the recitation of "mature polypeptide" was found persuasive in overcoming the 112, first paragraph rejections to the same. Moreover, Applicants specification explicitly supports the amino acid locations of the mature DmTNFv2 polypeptide as well as the nucleotide positions of the encoding polynucleotide of the mature DmTNFv2 polypeptide (see page 51). Applicants respectfully request that the Examiner withdraw the rejection of Claim 46 under 112, first paragraph in consideration of this error and the arguments provided herein.

Applicants do not agree with the Examiners rejection of Claim 48 under this title since Applicants clearly identified the location of the TNF domain which is explicitly denoted in Figures 3A-C as well as the legend of Figures 3A-C on page 11. Nonetheless, in the sole interest of facilitating prosecution, Applicants have cancelled Claim 48, its dependent Claim 49, as well as subpart (d) of Claim 41. Applicants believe the Examiners rejection of Claim 48 and Claim 41, in part, has been rendered moot in consideration of these cancellations.

Applicants also believe that the Examiners rejection of Claim 50, and also Claim 41(e) has also been rendered moot in consideration of Applicants deletion of clause (d) of Claim 41. Applicants point out that the Examiners original rejections specific to Applicants "complimentary sequence" claims were overcome in consideration of the arguments provided by Applicants in the August 6th, 2003 reply. Since the Claim 50 is dependent upon Claim 41(e), the fact that Claim 41(e) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly

or implicitly in the Examiners current and/or prior communications, Applicants believe the Examiners rejection of Claim 50 and Claim 41(e) has been overcome in consideration of Applicants deletion of clause (d) of Claim 41.

Applicants also believe that the Examiner rejection of Claim 51, and also Claim 41(f) has also been rendered moot in consideration of Applicants deletion of clause (d) of Claim 41, as well as Applicants amendment of Claim 41(f) to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed". Nonetheless, in an effort to further facilitate prosecution, Applicants have amended the phrase "(a)-(e)" of clause (f) of Claim 41 to recite the phrase "(a)-(c)". Since Claim 51 is dependent upon Claim 41(f), the fact that Claim 41(f) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly or implicitly in the Examiners current and/or prior communications, Applicants believe the Examiners rejection of Claim 51 and Claim 41(f) has been overcome in consideration of Applicants deletion of clause (d) of Claim 41 as well as the amendments presented *supra.*

Applicants believe the Examiners rejection of Claims 58 to 60 have also been overcome in consideration of the amendment to Claim 58 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" as well as the arguments presented *supra.* Applicants believe the specification provides adequate teachings to enable a skilled artisan to make and use the invention embraced by these claims as outlined in the arguments presented in Applicants August 6th, 2003 Reply. Since Claims 59 and 60 dependent from Claim 58, Applicants believe the Examiners rejection of Claims 59 and 60 have also been overcome.

Applicants believe the Examiners rejection of Claims 64 to 65 have also been overcome in consideration of Applicants deletion of clause (d) of Claim 41. Applicants point out that the Examiners original rejections specific to Applicants "complimentary sequence" claims were overcome in consideration of the arguments provided by Applicants in the August 6th, 2003 reply. Since Claim 64 is dependent upon Claim 41(e), the fact that Claim 41(e) is dependent upon clauses (a), (b), and (c), and the fact that Applicants possession and/or enablement for the subject matter of clauses (a), (b), and (c) has been affirmed by the Examiner either explicitly or implicitly in the

Examiners current and/or prior communications, Applicants believe the Examiners rejection of Claim 64 has been overcome in consideration of Applicants deletion of clause (d) of Claim 41.

V. Rejections under 35 U.S.C. § 102(b)

a. The Examiner has rejected Claims 41, 51, 58 and 62 under 35 U.S.C. § 102(b), alleging that these claims are anticipated by "Celniker et al (ACO05974, 1998)" and has maintained this rejection from the first Office Action. More particularly, the Examiner alleges that "Applicant argues that the fragment described in Celinker et al does not encode for TNF domain and thus does not TNF activity. As indicated above in paragraphs 10 and 11 it is not clear what TNF activity is contemplated by the Applicants. Therefore, the disclosure of Celniker et al., anticipates claims 41,51,58 and 62.".

Applicants do not agree with the Examiners assertion and point out that the Examiner did not fully consider all of Applicants arguments. Proper rejections under 35 U.S.C. § 102 specifically require that every element of a claim be taught by the cited reference. Since not all of the limitations of Claims 41, 51, 58, and 62 are taught by Celniker, it cannot properly be considered as an anticipating reference under 35 U.S.C. § 102.

Relative to Claims 41 and 51, Applicants argued that the ACO05974 reference only teaches a portion of the DmTNFv2 polynucleotide sequence (nucleotides 5 – 806 of SEQ ID NO:5), a portion that does not include the polynucleotides that encode the TNF domain, and thus would not be expected to have "TNF activity". However, in an effort to facilitate prosecution, Applicants have amended Claims 41 and 51 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Since the TNF domain is critical to the apoptotic activity of DmTNFv2, one skilled in the art would not expect that a sequence lacking this domain would have pro-apoptotic activity. Since the Celniker et al sequence lacks this domain, Applicants assert that it does not teach all of the limitations of Claims 41 and 51 and is not a proper reference under 35 U.S.C. § 102 and does not anticipate Claims 41 and 51. Applicants request that the Examiner withdraw the 102(b) rejection as it relates to Claims 41 and 51 in consideration of the amendments and arguments presented herein.

Relative to Claim 58, Applicants also pointed out to the Examiner that the sequence taught by Celniker et al is 158983 base pairs long. Since Claim 58 requires that the percent identity be determined using the CLUSTALW global alignment algorithm, an algorithm that takes into account gaps in assessing percent identity, the percent identity between the entire sequence taught by Celniker et al to any one of the sequences of Claim 41 would not be within the 80% identity threshold required by Claim 58. For example, the percent identity between the polynucleotide of Claim 41(a) and the Celniker et al sequence is less than 1% using CLUSTALW with default parameters (the sequences that flank the region within the Celniker et al sequence that match nucleotides 5 to 806 of SEQ ID NO:5 are considered as gaps by CLUSTALW and are thus assessed a significant gap penalty). Even in the instance where Celniker et al taught only the isolated sequence corresponding to nucleotides 5 to 806 of SEQ ID NO:5, the percent identity between that sequence to the sequence of Claim 41(a) is only 32.1% using CLUSTALW with default parameters. As a result, it is clear that the Celniker et al publication does not meet the "at least 80% identity" limitation of Claim 58. Moreover, Applicants also pointed out that Claim 58 requires that the polynucleotide encode a polypeptide that has "TNF activity". However, in an effort to facilitate prosecution, Applicants have amended Claim 58 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Based upon the arguments presented *supra* for Claims 41 and 51 regarding apoptotic activity, Celniker et al also does not anticipate this limitation. Since Celniker et al does not teach all of the limitations of Claim 58, Applicants assert that Celniker et al is not a proper reference under 35 U.S.C. § 102 and does not anticipate Claim 58. Applicants request that the Examiner withdraw the 102(b) rejection as it relates to Claims 58 in consideration of the amendments and arguments presented herein.

Relative to Claim 62, Applicants also argued that the ACO05974 reference only teaches a portion of the DmTNFv2 polynucleotide sequence (nucleotides 5 – 806 of SEQ ID NO:5), a portion that does not include the polynucleotides that encode the TNF domain, and thus would not be expected to have "TNF activity". However, in an effort to facilitate prosecution, Applicants have amended Claim 62 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants. Since the TNF domain is critical to the apoptotic

activity of DmTNFv2, one skilled in the art would not expect that a sequence lacking this domain would have pro-apoptotic activity. Since the Celniker et al sequence lacks this domain, Applicants assert that it does not teach all of the limitations of Claim 62. Moreover, since Claim 62 depends from Claim 41, it is clear that the Celniker et al sequence does not teach all of the limitations of Claim 41. Specifically, the Celniker et al sequence corresponds to only the amino acids 1 to 57 of SEQ ID NO:6 (see Applicants Figures 3A-C relative to the position of nucleotides 5 to 806 and the amino acid positions in which this region encodes). Since Claim 41 is directed to a polynucleotide sequence that encodes a polypeptide corresponding to amino acids 1 to 409 of SEQ ID NO:6, a polynucleotide sequence that encodes a polypeptide corresponding to amino acids 2 to 409 of SEQ ID NO:6, a polynucleotide sequence that encodes a mature polypeptide corresponding to amino acids 53 to 409 of SEQ ID NO:6, a polynucleotide sequence encoding the TNF domain of the DmTNFv2 polypeptide corresponding to amino acids 316 to 332 of SEQ ID NO:6, and the complimentary sequences of these sequences, it is clear that that the Celniker et al sequence does not teach all of the limitations of Claim 62. Specific to Claim 41(f), the argument provided for Claim 62 as well as Claims 41 and 51 *supra* relative to pro-apoptotic activity applies. Therefore, Celniker et al does not teach all of the limitations of Claim 62 and thus is not a proper reference under 35 U.S.C. § 102 and does not anticipate Claim 62. Applicants request that the Examiner withdraw the 102(b) rejection as it relates to Claims 62 in consideration of the amendments and arguments presented herein.

VI. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claims 41, 58, 62, 63, and 66 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claims 41, 58, 62, 63, and 66 as being "as vague and indefinite for reciting 'TNF activity'. It is unclear what TNF activity is contemplated by the Applicants".

Applicants disagree. However, in the interest of facilitating prosecution, Applicants have amended Claims 58, 62, 63, and 66 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants.

Moreover, Applicants have amended Claim 41(f) to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein the complimentary sequence of said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to clarify the activity originally intended by Applicants as well as to further clarify that only the complimentary sequence of the hybridized sequence would be expected to encode a pro-apoptotic polypeptide. Applicants believe the Examiner's rejection of Claims 41, 58, 62, 63, and 66 has been rendered moot in light of this amendment and request that this rejection be withdrawn.

VII. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected Claims 62, 63, and 66 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement. Specifically, the Examiner alleges that "the specification, while being enabling for a polypeptide of SEQ ID NO: 6 (amino acids 1 to 409 or amino acid 53-409), does not reasonably provide enablement for amino acid sequences of SEQ ID NO: 6 (amino acids 1-315, 316-332 and 333-409). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..."

Applicants disagree with the Examiners allegations and assert that the Examiner has misconstrued the scope of these claims and that this error has led to the Examiners enablement rejection. Applicants point out that Claim 62 is not directed to a polynucleotide fragment of DmTNFv2 that encodes amino acids 1 to 315 of SEQ ID NO:6 as alleged by the Examiner. Rather, Claim 62 is directed to N-terminal deletion mutants of DmTNFv2 that begin from the polynucleotides that encode amino acids 1 up to amino acid 315 of SEQ ID NO:6. Applicants note that SEQ ID NO:6 represents the full-length polypeptide sequence of DmTNFv2. Thus, this claim encompasses the polynucleotides encoding amino acids 1 to 409 with the exception that one or more of the polynucleotides encoding amino acids 1 up to amino acid 315 of the full-length polypeptide is deleted (e.g., polynucleotides encoding amino acids 2 to 409, polynucleotides encoding amino acids 3 to 409, polynucleotides encoding amino acids 4 to 409, etc.). Applicants also point out that the Examiner has explicitly stated that the polynucleotides encoding amino acids 1 to 409 is fully enabled. Since the TNF domain is maintained in each of the deletion mutants encompassed by this

claim, Applicants assert that one skilled in the art would credibly believe that each mutant would have "pro-apoptotic" activity. The Examiner should acknowledge this error and withdraw the rejection.

Applicants also point out that Claim 66 is not directed to a polynucleotide fragment of DmTNFv2 that encodes amino acids 333 to 409 of SEQ ID NO:6 as alleged by the Examiner. Rather, Claim 66 is directed to C-terminal deletion mutants of DmTNFv2 that begin from the polynucleotides that encode amino acids 409 up to amino acid 333 of SEQ ID NO:6. Applicants note that SEQ ID NO:6 represents the full-length polypeptide sequence of DmTNFv2. Thus, this claim encompasses the polynucleotides encoding amino acids 1 to 409, with the exception that one or more of the polynucleotides encoding amino acids 409 up to amino acid 333 of the full-length polypeptide is deleted (e.g., polynucleotides encoding amino acids 1 to 408, polynucleotides encoding amino acids 1 to 407, polynucleotides encoding amino acids 1 to 406, etc.). Applicants again point out that the Examiner has explicitly stated that the polynucleotides encoding amino acids 1 to 409 is fully enabled. Since the TNF domain is maintained in each of the deletion mutants encompassed by this claim, Applicants assert that one skilled in the art would credibly believe that each mutant would have "pro-apoptotic" activity. The Examiner should acknowledge this error and withdraw the rejection.

Applicants also point out that Claim 63 is not directed to a polynucleotide fragment of DmTNFv2 that encodes amino acids 316 to 332 of SEQ ID NO:6 as alleged by the Examiner. Rather, Claim 63 is directed to polynucleotides encoding amino acid substitution mutants of DmTNFv2 wherein the amino acid substitutions reside in the region beginning at amino acid 316 to 332 of SEQ ID NO:6. Applicants note that SEQ ID NO:6 represents the full-length polypeptide sequence of DmTNFv2. Thus, this claim encompasses the polynucleotides encoding amino acids 1 to 409, with the exception that one or more of the polynucleotides encoding amino acids 316 to amino acid 332 of the full-length polypeptide is substituted. Applicants point out again that the Examiner has explicitly stated that the polynucleotides encoding amino acids 1 to 409 is fully enabled. Since the TNF domain is maintained in each of these substitution mutants encompassed by this claim, Applicants assert that one skilled in the art would credibly believe that each mutant would have "pro-apoptotic" activity. The Examiner should acknowledge this error and withdraw the rejection.

Applicants also point out to the Examiner that each of the N-terminal deletion mutants embraced by Claim 62 is explicitly disclosed in the instant specification on pages 54 to 58.

Applicant's specification also teaches how to create such mutants in Example 9. Applicants assert that the genus encompassed by Claim 62 is adequately represented by Applicants disclosed species in sufficient detail to enable one skilled in the art to make and use the species in the claimed genus. In view of Fiers v. Revel, 984 F.2d, 1164 (Fed. Cir. 1993), Applicants assert that one skilled in the art could make and use the invention embraced by Claim 62 based upon the explicit disclosure of each of these sequences in the instant specification since one skilled in the art only requires the sequence of a molecule to make and use the same.

Applicants also point out to the Examiner that each of the C-terminal deletion mutants embraced by Claim 66 is explicitly disclosed in the instant specification on pages 54 to 58. Applicant's specification also teaches how to create such mutants in Example 9. Applicants assert that the genus encompassed by Claim 66 is adequately represented by Applicants disclosed species in sufficient detail to enable one skilled in the art to make and use the species in the claimed genus. In view of Fiers v. Revel, 984 F.2d, 1164 (Fed. Cir. 1993), Applicants assert that one skilled in the art could make and use the invention embraced by Claim 66 based upon the explicit disclosure of each of these sequences in the instant specification since one skilled in the art only requires the sequence of a molecule to make and use the same.

Applicants also point out to the Examiner that each of the substitution mutants embraced by Claim 63 is explicitly disclosed in the instant specification on pages 58 to 59. Applicant's specification also teaches how to create substitution mutants in Example 11. In addition, Applicants assert that one skilled in the art would readily appreciate how to create such mutants using methods well known in the art. Applicants further assert that the genus encompassed by Claim 63 is adequately represented by Applicants disclosed species in sufficient detail to enable one skilled in the art to make and use the species in the claimed genus. In view of Fiers v. Revel, 984 F.2d, 1164 (Fed. Cir. 1993), Applicants assert that one skilled in the art could make and use the invention embraced by Claim 63 based upon the explicit disclosure of each of these sequences in the instant specification since one skilled in the art only requires the sequence of a molecule to make and use the same.

The Examiner further also alleges that "It is unclear which fragments are required to confer the "TNF activity". It is also not clear what TNF activity is contemplated. Claims 62, 63 and 66 are describing three mutually exclusive amino acid fragments yet the three claims assert that they have TNF activity, for example, amino acids 1-315, 316-332 and 333-409. Despite knowledge in the art for producing polypeptides, the specification fails to provide any guidance regarding the proteins

produced by the contemplated amino acid fragments and yet retain the function is lacking. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. Therefore, predicting which amino acid fragments, if any, would retain the "TNF activity" of the protein is well outside the realm of routine experimentation. Thus, an undue amount of experimentation would be required to generate the changes/modifications contemplated and yet retain the function of the proteins claimed.".

Applicants disagree and point out again that the Examiner has misconstrued the scope of these claims and do not believe the Examiners rejection is proper on account of the errors discussed *supra*. Nonetheless, as Applicants noted in the August 6th, 2003 reply, Applicants specification teaches the location of the TNF domain of the DmTNFv2 polypeptide. Since the function of TNF family members is dependent upon the integrity of this domain, one skilled in the art would readily appreciate that the function of DmTNFv2 would be maintained if the amino acid deletions, or insertions resided outside of this domain. Applicants specification also teaches explicit conservative amino acid substitutions within the TNF domain that would preserve the function of the DmTNFv2 polypeptide (see page 32, and pages 58 to 60). Applicants assert that one skilled in the art would appreciate how to make and use the claimed invention based upon the teachings of the specification as originally filed. However, as discussed *supra*, Applicants have amended Claims 62, 63, and 66 to replace the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation with "wherein said polynucleotide encodes a polypeptide that induces apoptosis in a cell or tissue in which said polypeptide is recombinately expressed" in an effort to further clarify the activity originally intended by Applicants and to facilitate prosecution. Applicants believe the Examiner's rejection has been rendered moot in light of these amendments and request that this rejection be withdrawn.

Applicants also disagree that undue experimentation would be required to assess which changes/modifications of the claimed polynucleotides would retain DmTNFv2 function, particularly in light of the teachings of Applicants specification.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 443 F.2d 1386, 1390-91, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). As pointed out by the Examiner, the factors that can be considered in determining whether an amount of experimentation is undue have been set forth in In

re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. See id.

At the time of filing of the instant application, techniques were available for routinely generating substitutions, deletions, and insertions of polynucleotides. As discussed *supra*, Applicants specification even provides specific teachings that explicitly describes how one skilled in the art could make and use such substitutions, deletions, and insertions of the DmTNFv2 polynucleotide and polypeptide (see *supra*). Applicants also submit that Applicants specification also provides methods that could be used to specifically confirm whether a variant of the present invention retains DmTNFv2 activity (see Example 5, and pages 80 to 98). Applicants submit that the skilled protein molecular biologist, enlightened by the teaching of the present specification, was more than capable of routinely determining whether a polynucleotide encoding a polypeptide encompassed by the claims displays TNF activity.

Applicants submit that because of: (1) the availability of routine techniques for creating mutant polynucleotides; (2) the knowledge of the location of the TNF domain of DmTNFv2; (3) the sequence of the DmTNFv2 polynucleotide and polypeptide; (4) the availability of routine techniques for assaying for TNF activity of DmTNFv2 polypeptides; (5) the high level of skill in the field of protein chemistry and molecular biology; and (6) the direction and guidance provided by the specification regarding specific methods to be employed to create and assess the TNF activity of DmTNFv2 variants, one skilled in the art could routinely generate the claimed polypeptides and determine whether these variants exhibit TNF activity and satisfy the limitations recited in the claims.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A three-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $950 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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